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TRANSMITTAL LETTER (General - Patent Pending)	Docket No. RU-0115

In Re Application Of: **Anders n et al.**

Serial No.	Filing Date	Examiner	Group Art Unit
09/744,002	August 2, 2001	Jeffrey Norman Fredman	1634

Title: **LINKING GENE SEQUENCE TO GENE FUNCTION BY THREE DIMENSIONAL (3D) PROTEIN STRUCTURE DETERMINATION**

TO THE COMMISSIONER FOR PATENTS:

Transmitted herewith is:

Appeal Brief (Small Entity)
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Jane Massey Licata
Signature

Dated: **September 16, 2003**

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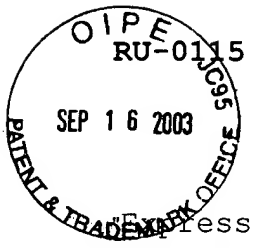

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1) General Transmittal Letter (in triplicate);

2) Appeal Brief (in triplicate);

3) Return Post Card; and

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Jane Massey Licata

JANE MASSEY LICATA

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No.:	**RU-0115**
Inventors:	**Anderson et al.**
Serial No.:	**09/744,002**
Filing Date:	**August 2, 2001**
Examiner:	**J. Fredman**
Group Art Unit:	**1634**
Title:	**Linking Gene Structure to Gene Function by Three Dimensional (3D) Protein Structure Determination**

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By _____
Typed Name: **Jane Massey Licata**, Reg. No. **32,257**

Commissioner for Patents
Mail Stop AF
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

APPEAL BRIEF

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Table of Contents

I. Real Party of Interest

The real party of interest is Rutgers, The State University, assignee of all rights, title and interest in the instant application.

II. Related Appeals and Interferences

A Notice of Appeal has been filed in the parent application of this case, U.S. Application No. 09/181,601, filed October 29, 1998, the case to which the instant application claims priority.

III. Status of Claims

Claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 13 are pending.

Claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 13 are rejected.

A copy of pending claims 1 through 13 is attached hereto as Appendix 1.

IV. Status of Amendments

All amendments to the claims submitted by Appellants during prosecution of this case have been entered upon this appeal. Appellants have attached hereto as Appendix 2 a claim set of claims 1 through 13 incorporating proposed amendments as discussed below in the section entitled **Arguments**.

V. Summary of the Invention

The claimed invention is a method for elucidating the function of proteins and protein domains by generating and examining their three dimensional structures, and more specifically by the use of bioinformatics, molecular biology and nuclear magnetic resonance spectroscopy to enable the rapid and automated determination of functions, as a means for genome analysis. In this method, the first step of the instant method involves identifying a putative polypeptide domain that properly folds into a stable polypeptide domain having a defined three dimensional structure. This identification step involving a domain is taught at pages 11-18 and Figure 1 of the specification as filed. In the second step of the claimed method, the three dimensional structure of the stable polypeptide domain is then determined. Methods for determining the three dimensional structure of the stable polypeptide domain are taught at pages 3-5 and pages 24-25, and include the preferred method NOESY-Assign process, as well as other methods for analysis of NMR data. The next step involves comparing the determined three dimensional structure of the stable polypeptide domain to known three dimensional structures in a protein data bank in order to identify known structures within the protein data bank that may be homologous to the determined three dimensional structure. This step in the method is discussed at page 26. The final step in the claimed method involves correlating a biochemical function

corresponding to the identified homologous structure to a biochemical function for the stable polypeptide domain. This part of the method is described at pages 26-28. Further, the method of the present invention is shown graphically as a flow chart in Figure 1.

VI. Issues

The issues on appeal are :

1) whether the claims of the instant application can properly receive the benefit of priority to the parent application 09/181,601;

2) whether claim 12 is anticipated by 35 U.S.C. 102(b) as being anticipated by the University of Texas at Galveston as evidenced by Mumenthaler et al. (1995);

3) whether claims 1, 5 and 11 are unpatentable under 35 U.S.C. § 103(a) as being obvious over Wallace et al. (1996), in view of Mumenthaler et al. (1995);

4) whether claims 1-5 and 11 are unpatentable under 35 U.S.C. § 103(a) as being obvious over Wallace et al. (1996), in view of Mumenthaler et al. (1995), and further in view of Farber et al. (1992);

5) whether claims 1, 5, 6 and 11 are unpatentable under 35 U.S.C. § 103(a) as being obvious over Wallace et al. (1996), in

view of Mumenthaler et al. (1995), and further in view of Friedrichs et al. (1994);

6) whether claims 1, 5, 7 and 11 are unpatentable under 35 U.S.C. § 103(a) as being obvious over Wallace et al. (1996), in view of Mumenthaler et al. (1995), and further in view of Bagby et al. (1997);

7) whether claims 1, 5 and 8-11 are unpatentable under 35 U.S.C. § 103(a) as being obvious over Wallace et al. (1996), in view of Mumenthaler et al. (1995), and further in view of Holm et al. (1995); and

8) whether claims 1, 5, 8-11 and 13 are unpatentable under 35 U.S.C. § 103(a) as being obvious over Wallace et al. (1996), in view of Mumenthaler et al. (1995), and further in view of Holm et al. (1995) and Farber et al. (1992).

VII. Grouping of Claims

Claims 1 through 13 stand or fall together on the issue of priority and the issues of obviousness under 35 U.S.C. § 103(a), considering any combination of the cited art. Claim 12 stands and falls alone on the issue of anticipation under 35 U.S.C. § 102(b).

VIII. Arguments

A. Priority

Priority to parent application Serial No. 09/181,601 has not been granted because the Examiner suggests that the parent application lacks descriptive support for the element of "NOESY-assign process". The Examiner suggests that the claims as filed in the instant application are not supported by the parent application. Appellants respectfully disagree with the Examiner's conclusions regarding the benefit of priority.

1. MPEP § 201.08 Allows for Addition of Matter Not Disclosed in the Parent Application

The instant application is a continuation-in-part of the parent application Serial No. 09/181,601. MPEP § 201.08 states that a continuation-in-part may be filed during the lifetime of an earlier nonprovisional application, repeating some substantial portion or all of the earlier nonprovisional application and *adding matter not disclosed* in the said earlier nonprovisional application. The Examiner has suggested, however, that there is no support for the matter added in the instant application, namely the "NOESY-Assign process". Appellants respectfully disagree with the Examiner's assertion that there is no support in the parent application for the matter claimed in instant claims 1-13.

The current application shares a substantial portion of content and as well as most of the exact wording of the claims of the parent application 09/181,601. In particular, the steps of determining a biochemical function of a protein or polypeptide domain are identical. Both applications share the basic steps of identifying a putative polypeptide domain; determining three dimensional structure of the stable polypeptide domain; comparing the determined three dimensional structure of the stable polypeptide domain to known three-dimensional structures in a protein data bank; and correlating a biochemical function corresponding to the identified homologous structure to a biochemical function for the stable polypeptide domain. The limitation of "NOESY-assign process", which was added to claim 1 of this continuation-in-part application, is merely one of many means of **determining the three dimensional structure of the stable polypeptide domain.** Therefore, the NOESY-Assign process, claimed in the continuation-part-application, is one means of "determining the three dimensional structure of the stable polypeptide domain", and was claimed separately in the claims of the instant application as it is the preferred embodiment. Therefore, this continuation-part-application, although disclosing a different means for "determining the three dimensional structure of the stable polypeptide domain", is

entitled to the benefit of priority of the parent application as the parent and instant invention are both drawn to a method of determining biochemical function of a protein or polypeptide domain of unknown function, and both rely on the same step, "determining the three dimensional structure of the stable polypeptide domain", only using different preferred embodiments.

B. Rejection of Claims Under 35 U.S.C. 102(b)

The Examiner has rejected claim 12 under 35 U.S.C. 102(b) as being anticipated by the University of Texas at Galveston as evidenced by Mumenthaler et al. (1995). The Examiner suggests that this campus comprised a computer, an NMR facility with a spectrometer, a data collection device, and computer algorithms to analyze NMR spectra and determine tertiary structure of proteins, including the NOAH program for automated assignment of NOESY spectra, as well as laboratories for expression proteins, access to the Wisconsin programs for parsing target polynucleotides, and Internet access to the Protein Data Bank and the DALI webserver.

1. Summary of the Teachings of the Cited Reference

The University of Texas at Galveston, as evidenced by Mumenthaler et al. (1995) disclose a method for automatically assigning proton-proton NOESY spectra in reference to proteins

of **known function**, specifically dendrotoxin K, α-amylase inhibitor tendamistat, and the DNA-binding domain of the 434 repressor protein. Nowhere does the paper of Mumenthaler et al. teach or suggest the steps of parsing a target polynucleotide into at least one putative domain encoding region nor subsequently expressing said putative domain on which to conduct NMR analysis. Moreover, the proteins analyzed by Mumenthaler et al. had **known functions** to which a three dimensional protein structure was assigned.

2. The Cited Reference Fails to Teach the Limitations of the Claims

In accordance with MPEP § 2131, the reference must teach and every element of the claim in order to anticipate the claim. Mumenthaler et al. do not teach every element of the claimed method. As stated *supra*, this reference fails to teach or suggest the steps of parsing a target polynucleotide into at least one putative domain encoding region and subsequently expressing said putative domain on which to conduct NMR analysis. Further, the paper of Mumenthaler deals only with examining proteins with known functions. In contrast, claim 12 is directed toward the determination of a biological function of a protein or protein domain of **unknown function**. Nowhere, do Mumenthaler et al. teach or suggest a

method for determining biochemical function of a protein or polypeptide domain of **unknown function.** Since Mumenthaler et al. do not teach a method wherein polypeptide domains are identified and expressed and the unknown function of said domain is determined, this reference cannot anticipate claim 12.

However, in an earnest effort to make the claimed invention more clear, Appellants have provided in Appendix 2 a proposed amendment to claim 12 wherein an explicit characteristic has been added that lists a sample containing a protein of unknown function.

C. Rejection of Claims Under 35 U.S.C. 103(a)

There are six pending rejections under 35 U.S.C. 103(a) and each rejection relies on the same primary reference (Wallace et al. 1996). The six separate rejections then involve six different combinations of secondary references.

The Examiner has rejected claims 1, 5 and 11 under 35 U.S.C. § 103(a) as being unpatentable over Wallace et al. (1996), in view of Mumenthaler et al. (1995). The Examiner suggests that it would have been *prima facie* obvious to one of ordinary skill in the art at the time this invention was made to combine the 3-D structural alignment and function determination method of Wallace et al. with the NOESY assignment method of Mumenthaler et al. since Mumenthaler

et al. state "We regard our method as a highly practical tool for automatic calculation of three dimensional protein structures from NMR spectra with minimal human interface (abstract)". The Examiner suggests that an ordinary practitioner would have been motivated to determine the 3-D structures used by Wallace et al. for analysis by the automated method of Mumenthaler et al. since the method is a highly practical tool which results "In practice, the work required to assign NOESY spectra is dramatically reduced by applying our automated method (page 466, column 2)".

Claims 1-5 and 11 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Wallace et al. (1996) in view of Mumenthaler et al. (1995) and further in view of Farber et al. (1992). The Examiner suggests that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Wallace et al. in view of Mumenthaler et al. with the database preparation method of Farber et al. since Farber et al. note "Simple neural networks predict coding regions in DNA very well when trained on representation of DNA using single codon frequencies (Page 478, column 1)." The Examiner suggests that an ordinary practitioner would have been motivated to combine the method of Wallace et al. in view of Mumenthaler et al. with the protein coding determinations of Farber et al. in order to maximize the usable

databases to identify homologous proteins and thereby determine the function of unknown proteins.

Claims 1, 5, 6 and 11 have also been rejected under 35 U.S.C. § 103(a) as being unpatentable over Wallace et al. (1996) in view of Mumenthaler et al. (1995) and further in view of Friedrichs et al. (1994). The Examiner suggests that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the 3-D structural alignment and function determination method of Wallace et al. in view of Mumenthaler et al. with the use of NMR structural determination of Friedrichs et al. since Wallace et al. state "This suggests that the development of databases of 3-D templates, such as those that currently exist for protein sequence templates, will help identify the functions of new protein structures as they are determined and pinpoint their functionally important regions (abstract)". The Examiner suggests that the ordinary practitioner would have been motivated to utilize NMR to determine protein structures in order to sensitively and accurately provide data for 3-D determinations and would have been motivated to utilize the automated assignments of Friedrichs et al. in order to minimize the time needed to determine the 3-D structure as expressly motivated by Friedrichs et al.

Claims 1, 5, 7 and 11 have also been rejected under 35 U.S.C. § 103(a) as being unpatentable over Wallace et al. (1996) in view

of Mumenthaler et al. (1995) and further in view of Bagby et al. (1997). The Examiner suggests that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the button test of Bagby et al. with the NMR and functional determination method of Wallace et al. in view of Mumenthaler et al. since Bagby et al. state "The button test is an efficient, small scale way of tackling this problem (page 281, column 1)". The Examiner suggests that the ordinary practitioner would have been motivated to utilize the button test to optimize solubility for NMR since it is expressly noted as efficient and small scale, which reduced time and wasted reagents, which for purified proteins can represent a large investment of time and money.

Claims 1, 5 and 8-11 have also been rejected under 35 U.S.C. § 103(a) as being unpatentable over Wallace et al. (1996) in view of Mumenthaler et al. (1995) and further in view of Holm et al. (1995). The Examiner suggests that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the 3-D structural alignment and function determination method of Wallace et al. in view of Mumenthaler et al. with the NMR technique taught by Holm et al. and well known in the art for structure determination purposes and with the use of domains within the range of 50-300 amino acids since Holm et al. teach screening domain of those sizes. The Examiner

suggests that the ordinary practitioner would have been motivated to utilize database analysis of Holm et al. in mind of Wallace et al. since Wallace et al. state "As the number of known protein structures increases, so the need for a 3-D equivalent of PROSITE grows with it, especially for likely functions of proteins whose biological role is unknown (page 1001, column 1)." Further, Wallace et al. note that there is a need for methods of 3-D comparison of proteins in order to determine the biochemical function of unknown proteins. Holm et al. state "At the last stages of solving a new protein structure, crystallographers and nuclear magnetic resonance (NMR) spectroscopists are keen to know if their structure represents a unique protein fold or if it has an unexpected structural similarity to a known protein fold. To answer these questions, the DALI server performs a database search with a new structure against all structures in the Protein Data Bank (Page 478, column 3)". Thus, the Examiner further suggests that the ordinary practitioner would have been motivated to perform a comparison to determine the relationship of the new protein with proteins present in the database, thereby fulfilling the stated need and motivation of Wallace et al.

Claims 1, 5, 8-11 and 13 have also been rejected under 35 U.S.C. § 103(a) as being unpatentable over Wallace et al. (1996) in view of Mumenthaler et al. (1995) and further in view of Holm et al. (1995) and further in view of Farber et al. (1992). The

Examiner suggests that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Wallace et al. in view of Mumenthaler et al. and further in view of Holm et al. with the database preparation method of Farber et al. since Farber et al. note "Simple neural networks predict coding regions in DNA very well when trained on a representation of DNA using single codon frequencies (page 478, column)." The Examiner further suggests that the ordinary practitioner would have been motivated to combine the method of Wallace et al. in view of Mumenthaler et al. and further in view of Holm et al. with the protein coding determinations of Farber et al. in order to maximize the usable databases to identify homologous proteins and thereby determine the function of unknown proteins.

Appellant respectfully disagrees with the Examiner's suggestions regarding each of the six rejections under 35 U.S.C. 103(a) that are on appeal.

1. Summary of the Teachings of Each Reference Cited Under 35 U.S.C. 103(a)

The primary reference of Wallace et al. does not teach an essential step in the methods of the instant claims, namely the identification of a protein or polypeptide domain that properly folds into a stable polypeptide domain with a defined

three dimensional structure. Nor is there any suggestion of this step, as Wallace et al. (1996) teach derivation of 3-dimensional coordinate templates that have been derived from known 3-dimensional protein structures which are provided in a database. The paper then teaches determination of biochemical function based on the existence of the known 3-dimensional structures. The critical step in the method is the identification of a triad of amino acids (*e.g.*, Ser-His-Asp), that occur in a 3-dimensional configuration to form an active site or "domain". This "domain" concept is completely different from the structural domain concept taught in the instant application. Moreover, no other size of a putative domain is taught or suggested by this reference. In fact, it is this 3 amino acid sequence that is then used to guide identification of the functions of the unknown proteins as the authors report that this triad (3 amino acid domain) is what is critical for differentiating catalytic from non-catalytic proteins among the serine proteases and lipases. Further, as the authors state at page 1002, last paragraph in the first column, their method had specific steps that involved using a data set of serine proteases and lipases to automatically compute a highly specific 3D template for the Ser-His-Asp catalytic triad in the set of proteins. As they also state at page 1002, top of the second column, their method differed

from other previous methods as a simple template specific to the Ser-His-Asp catalytic triad is derived. Then, the next step was to search for similar triads in other proteins to see how often they occurred outside of the serine proteases and lipases. Thus, the teaching of this paper is limited to teaching a skilled artisan that databases may be searched using a specific 3D template, the triad, and then used to identify a potential biological function of a protein with an **unknown structure**. Nowhere does this paper teach or suggest determination of the unknown structure of a protein of **unknown function**. Therefore, this primary reference fails to teach the limitations of independent claim 1, and teaches away from essential elements of claim 1.

Further, nowhere does the primary reference teach or provide the skilled artisan with the motivation to take a single- or multi-domain protein or polypeptide of unknown function and identify each individual domain of said protein or polypeptide. Thus, the primary reference also fails to provide any teaching or suggestion of the system of independent claim 13 which comprises the identification of at least one putative polypeptide domain (element A) prior to the steps of expressing the domain and determining its three dimensional structure.

Accordingly, this primary reference, which is the foundation for rejection of two of the independent claims, claims 1 and 13, fails to teach the limitations of those claims.

Mumenthaler et al. (1995) disclose a method for automatically assigning proton-proton NOESY spectra in reference to proteins of **known function**, specifically dendrotoxin K, α-amylase inhibitor tendamistat, and the DNA-binding domain of the 434 repressor protein. Nowhere does the paper of Mumenthaler et al. teach or suggest the essential step of identifying protein or polypeptide domains. Moreover, the proteins analyzed by Mumenthaler et al. had **known functions** to which a three dimensional protein structure was assigned.

Holm et al. (1995) is a commentary article wherein the DALI method is disclosed as being useful for the study of protein structure. In this method, structural relatedness is measured in terms of similarities of intramolecular distance matrices. The importance of this new automated method is discussed. However, this paper fails to teach a method which has any specific steps at all. Accordingly, this reference provides no teaching or suggestion with respect to either identification of protein or polypeptide domains or the

determination of unknown function of unknown three-dimensional protein structures as claimed in the instant invention.

Farber et al. (1992) disclose a neural network and information theory for determination of coding regions of DNA sequence. This paper, from a different art area (not protein biochemistry as is the area of one of skill in the instant invention), fails to teach or suggest a method such as the claimed invention. Nowhere is there any teaching or suggestion of the identification of protein or polypeptide domains. Moreover, being in a different art area, this paper would not be one that would be used by one of skill in protein biochemistry as motivation to produce the method of the instant invention. Only the hindsight vision afforded by the claimed invention would motivate the skilled practitioner to combine the teachings of Farber et al. with any of the other cited references from the protein biochemistry area (*e.g.*, Wallace et al.)

Friedrichs et al. (1992) is a review type paper that teaches an automated NMR procedure for protein ^{15}N, ^{13}C, and ^{1}H NMR resonance assignments from a set of three-dimensional NMR spectra. While resonance assignments are useful in establishing the three dimensional structure of protein, this information alone is insufficient for three dimensional structure determination. This paper fails to teach or suggest

a method with specific steps such as is claimed in the instant invention. In particular, there is no teaching with respect to either identification of protein or polypeptide domains or the process of determining the 3D structure of a protein, or the determination of unknown function of unknown three-dimensional protein structures as claimed in the instant invention.

Bagby et al. (1997) teaches methods for preparing samples for NMR analysis, specifically a button test method. This method is used by the authors to screen solution conditions to determine conditions under which a protein is soluble at high concentrations that are used for NMR spectroscopy. This paper fails to teach or suggest a method with specific steps such as is claimed in the instant invention. In particular, this paper fails to teach the identification of protein or polypeptide domains, or the process of determining the 3D structure of a protein, or the determination of unknown function of unknown three-dimensional protein structures as claimed in the instant invention.

Therefore, Appellant respectfully disagrees with the Examiner's suggestion that any combination of these prior art references establishes a *prima case* of obviousness.

2. If an Independent Claim is Nonobvious Then a Claim Depending Therefrom is Nonobvious (MPEP 2143.03)

Appellants point out as well that under MPEP 2143.03, "If an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious (In re Fine, 837 F.2d 1071, 5 USPQ2d 1596, Fed. Cir. 1988)." Thus, while some of the secondary references may teach or suggest specific elements as set forth in the dependent claims, the cited combination of references fail to teach or suggest all the limitations of the method or system as set forth in independent claims 1, 12 and 13.

3. Three Basic Criteria of *prima facie* Obviousness

In accordance with MPEP § 2143, to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the reference itself or in the knowledge generally available to one of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all of the claim limitations. The prior art combinations cited under 35 U.S.C. 103 by the Examiner fail to teach or suggest all of the limitations of the claims and fail to provide either the

motivation to modify the reference or the expectation of success.

4. The Cited Art Fails to Teach the Limitations of the Claims

Any of the combinations of prior art fail to teach or suggest the limitations in the claims. In particular, and as discussed *supra*, none of the cited references, either alone or when combined, teach the determination of the function of a protein of **unknown function** wherein this is accomplished by determining the structure of the protein and then correlating the structure with a function when the function is also unknown. Both the MPEP and case law are quite clear. To establish *prima facie* obviousness of a claimed invention, all the limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974) and MPEP 2143.03.

5. The Combined References Fail to Provide Motivation

The cited combinations of references also fail to establish a *prima facie* case of obviousness because the motivation to combine these references is lacking. The teaching or suggestion must be found in the prior art and not based on applicant's disclosure. In re Vacek, 947 F.2d 488,

20 USPQ2d 1438 (Fed. Cir. 1991). The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art suggests the desirability of the combination. MPEP § 2143.01. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). Wallace et al. is a protein biochemistry article directed at the analysis of protein structure and function. Contrary to the Examiner's suggestion, it would not have been obvious to the ordinary protein biochemist after reading Wallace et al. to take the additional steps provided by Farber et al. of mining a polynucleotide database. Furthermore, the combination of Wallace et al. with Farber et al. still does not provide the essential step of identifying protein or polypeptide domains. Moreover, the "catalytic triad domain" described by Wallace et al. is distinct from the overall "structural domains" of the instant invention. Thus, Farber et al. alone is insufficient for determination of unknown function of unknown three-dimensional protein structures as claimed in the instant invention.

Therefore, solely on the basis of the requirements for establishing a *prima facie* case of obviousness (MPEP 2143), any of the combinations of the cited references fail to make obvious any of the pending claims.

6. The Cited References Fail to Provide a Reasonable Expectation of Success

The primary reference cited in each of the six obviousness rejections, Wallace et al. (1996), is also important in that it would actually teach away from an expectation of success for the present method. The method of Wallace et al. is based on the importance of the identification of the triad domain. It is only with use of this domain as a screening tool that the authors report any success at correlating structure of a protein with a function. The present method, however, is not based on this triad, and in fact is based on a very different type of domain. Accordingly, this primary reference wold lead one of skill to not expect success using the current method which is not limited to use of the triad disclosed by Wallace et al.

Therefore, solely on the basis of the requirements for establishing a *prima facie* case of obviousness (MPEP 2143), these combined references, in any cited combination, fail to make obvious any of the pending claims.

IX. Conclusion

The references cited by the Examiner clearly do not provide the requisite teaching or suggestion to render the claimed invention of claims 1-11 or 13 obvious. Further the reference

cited by the Examiner fails to anticipate claim 12. Finally, Appellants respectfully disagree with the Examiner's conclusions regarding the assignment of priority and request reconsideration of the benefit of priority.

Respectfully submitted,

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Date: **September 16, 2003**

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Appendix 1 - Pending Claims

Claim 1: A high-throughput method for determining the biochemical function of a protein or polypeptide domain of unknown function comprising:

(A) identifying a putative polypeptide domain that properly folds into a stable polypeptide domain, said stable polypeptide domain having a defined three dimensional structure;

(B) determining three dimensional structure of the stable polypeptide domain from an automated analysis of NMR spectrometer spectra of said polypeptide domain, wherein said automated analysis is conducted by a NOESY-Assign process;

(C) comparing the determined three dimensional structure of the stable polypeptide domain to known three-dimensional structures in a protein data bank, wherein said comparison identifies known structures within said protein data bank that are homologous to the determined three dimensional structure; and

(D) correlating a biochemical function corresponding to the identified homologous structure to a biochemical function for the stable polypeptide domain.

Claim 2: The method of claim 1, further comprising the pre-step of parsing a target polynucleotide into at least one putative polypeptide domain.

Claim 3: The method according to claim 2, wherein said parsing is performed by a first computer algorithm, wherein said first computer algorithm is selected from the group consisting of a computer algorithm capable of determining exon phase boundaries of a polynucleotide, and a computer algorithm capable of determining interdomain boundaries encoded in a polynucleotide.

Claim 4: The method of claim 3, further comprising a computer algorithm that compares the putative polypeptide domain sequence with known domain sequences stored within a database.

Claim 5: the method of claim 1, wherein said NMR spectra are analyzed by a second computer algorithm that automatically assigns resonance assignments to the polypeptide sequence.

Claim 6: The method of claim 1, wherein said identification of said stable polypeptide domain comprises measuring the time course of amide hydrogen-deuterium exchange.

Claim 7: The method of claim 1, wherein prior to step (B), said stable polypeptide domain is optimally solubilized, said optimum solubilization comprising:

I) preparing an array of microdialysis buttons, wherein each of said microdialysis buttons contains at least 1 µl of an approximately 1 mM solution of said stable polypeptide domain;

ii) dialyzing each member of said array of microdialysis buttons against a different dialysis buffer;

iii) analyzing each of said dialyzed microdialysis buttons to determine whether said stable polypeptide domain has remained soluble; and

iv) selecting the polypeptide domain having optimum solubility characteristics for NMR spectroscopy.

Claim 8: The method of claim 1, wherein said comparison of said determined three dimensional structure to said three dimensional structures in the protein data bank is performed by a third computer algorithm that is capable of determining 3D structure homology between said determined three dimensional structure and a member of said PDB.

Claim 9: The method of claim 8, wherein said third computer algorithm is selected from the group consisting of DALI, CATH and VAST.

Claim 10: The method of claim 1, wherein said protein data bank is Protein Data Base ("PDB").

Claim 11: The method of claim 4, wherein said database contains domain sequence information of known and determined domain sequences.

Claim 12: An integrated system for rapid determination of a biochemical function of a protein or protein domain of unknown function:

(A) a first computer algorithm capable of parsing said target polynucleotide into at least one putative domain encoding region;

(B) a designated lab for expressing said putative domain;

(C) an NMR spectrometer for determining individual spin resonances of amino acids of said putative domain;

(D) a data collection device capable of collecting NMR spectral data, wherein said data collection device is operatively coupled to said NMR spectrometer;

(E) at least one computer;

(F) a second computer algorithm capable of assigning individual spin resonances to individual amino acids of a polypeptide;

(G) a third computer algorithm capable of determining tertiary structure of a polypeptide, wherein said polypeptide has had resonances assigned to individual amino acids of said polypeptide;

(H) a database, wherein stored within said database is information about the structure and function of known proteins and determined proteins; and

(I) a fourth computer algorithm capable of determining 3D structure homology between the determined three dimensional structure of a polypeptide of unknown function to three dimensional structure of a protein of known function, wherein said protein of known structure is stored within said protein database, wherein said fourth computer algorithm determines said structure by an automated NOESY-Assign process.

Claim 13: A high-throughput method for determining a biochemical function of a polypeptide of unknown function encoded by a target polynucleotide comprising the steps:

(A) identifying at least one putative polypeptide domain encoding region of the target polynucleotide ("parsing");

(B) expressing said putative polypeptide domain;

(C) determining whether said expressed putative polypeptide domain forms a stable polypeptide domain having a defined three dimensional structure ("trapping");

(D) determining the three dimensional structure of the stable polypeptide domain by an automated NOESY-Assign process;

(E) comparing the determined three dimensional structure of the stable polypeptide domain to known three dimensional structures in a Protein Data Bank to determine whether any such known structures are homologous to the determined structure; and

(F) correlating a biochemical function corresponding to the homologous structure to a biochemical function for the stable polypeptide domain.

Appendix 2 - Proposed Amendments to Claims 1, 12 and 13

Claim 1: A high-throughput method for determining the biochemical function of a protein or polypeptide domain of unknown function comprising:

(A) obtaining a sample comprising a protein of unknown function and identifying a putative polypeptide domain within said protein that properly folds into a stable polypeptide domain, said stable polypeptide domain having a defined three dimensional structure;

(B) determining three dimensional structure of the stable polypeptide domain from an automated analysis of NMR spectrometer spectra of said polypeptide domain, wherein said automated analysis is conducted by a NOESY-Assign process;

(C) comparing the determined three dimensional structure of the stable polypeptide domain to known three-dimensional structures in a protein data bank, wherein said comparison identifies known structures within said protein data bank that are homologous to the determined three dimensional structure; and

(D) correlating a biochemical function corresponding to the identified homologous or analogous structure to a biochemical function for the stable polypeptide domain.

Claim 2: The method of claim 1, further comprising the pre-step of parsing a target polynucleotide into at least one putative polypeptide domain.

Claim 3: The method according to claim 2, wherein said parsing is performed by a first computer algorithm, wherein said first computer algorithm is selected from the group consisting of a computer algorithm capable of determining exon phase boundaries of a polynucleotide, and a computer algorithm capable of determining interdomain boundaries encoded in a polynucleotide.

Claim 4: The method of claim 3, further comprising a computer algorithm that compares the putative polypeptide domain sequence with known domain sequences stored within a database.

Claim 5: the method of claim 1, wherein said NMR spectra are analyzed by a second computer algorithm that automatically assigns resonance assignments to the polypeptide sequence.

Claim 6: The method of claim 1, wherein said identification of said stable polypeptide domain comprises measuring the time course of amide hydrogen-deuterium exchange.

Claim 7: The method of claim 1, wherein prior to step (B), said stable polypeptide domain is optimally solubilized, said optimum solubilization comprising:

I) preparing an array of microdialysis buttons, wherein each of said microdialysis buttons contains at least 1 µl of an approximately 1 mM solution of said stable polypeptide domain;

ii) dialyzing each member of said array of microdialysis buttons against a different dialysis buffer;

iii) analyzing each of said dialyzed microdialysis buttons to determine whether said stable polypeptide domain has remained soluble; and

iv) selecting the polypeptide domain having optimum solubility characteristics for NMR spectroscopy.

Claim 8: The method of claim 1, wherein said comparison of said determined three dimensional structure to said three dimensional structures in the protein data bank is performed by a third computer algorithm that is capable of determining 3D structure homology between said determined three dimensional structure and a member of said PDB.

Claim 9: The method of claim 8, wherein said third computer algorithm is selected from the group consisting of DALI, CATH and VAST.

Claim 10: The method of claim 1, wherein said protein data bank is Protein Data Base ("PDB").

Claim 11: The method of claim 4, wherein said database contains domain sequence information of known and determined domain sequences.

Claim 12: An integrated system for rapid determination of a biochemical function of a protein or protein domain of unknown function consisting of:

(A) a first computer algorithm capable of parsing ~~said~~ a target polynucleotide encoding a protein of unknown function into at least one putative domain encoding region;

(B) a designated lab for expressing said putative domain;

(C) an NMR spectrometer for determining individual spin resonances of amino acids of said putative domain;

(D) a data collection device capable of collecting NMR spectral data, wherein said data collection device is operatively coupled to said NMR spectrometer;

(E) at least one computer;

(F) a second computer algorithm capable of assigning individual spin resonances to individual amino acids of a polypeptide;

(G) a third computer algorithm capable of determining tertiary structure of a polypeptide, wherein said polypeptide has had resonances assigned to individual amino acids of said polypeptide;

(H) a database, wherein stored within said database is information about the structure and function of known proteins and determined proteins; and

(I) a fourth computer algorithm capable of determining 3D structure homology between the determined three dimensional structure of ~~a~~ said polypeptide encoding said protein of unknown function to the known three dimensional structure of a polypeptide encoding a protein of known function, wherein said protein of known structure is stored within said protein

database, wherein said fourth computer algorithm determines said structure by an automated NOESY-Assign process.

Claim 13: A high-throughput method for determining a biochemical function of a ~~polypeptide~~ protein of unknown function encoded by a target polynucleotide comprising the steps:

(A) obtaining a sample of a target protein of unknown function and identifying at least one putative polypeptide domain encoding region of the target ~~polynucleotide~~ protein ("parsing");

(B) expressing said putative polypeptide domain;

(C) determining whether said expressed putative polypeptide domain forms a stable polypeptide domain having a defined three dimensional structure ("trapping");

(D) determining the three dimensional structure of the stable polypeptide domain by an automated NOESY-Assign process;

(E) comparing the determined three dimensional structure of the stable polypeptide domain to known three dimensional structures in a Protein Data Bank to determine whether any such known structures are homologous to the determined structure; and

(F) correlating a biochemical function corresponding to the homologous structure to a biochemical function for the stable polypeptide domain.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Inventors:	**Anderson et al.**
Serial No.:	**09/744,002**
Filing Date:	**August 2, 2001**
Examiner:	**J. Fredman**
Group Art Unit:	**1634**
Title:	**Linking Gene Structure to Gene Function by Three Dimensional (3D) Protein Structure Determination**

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Typed Name: **Jane Massey Licata,** Reg. No. **32,257**

Commissioner for Patents
Mail Stop AF
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Alexandria, VA 22313-1450

Dear Sir:

APPEAL BRIEF

Table of Contents

I. Real Party of Interest

The real party of interest is Rutgers, The State University, assignee of all rights, title and interest in the instant application.

II. Related Appeals and Interferences

A Notice of Appeal has been filed in the parent application of this case, U.S. Application No. 09/181,601, filed October 29, 1998, the case to which the instant application claims priority.

III. Status of Claims

Claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 13 are pending.

Claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 13 are rejected.

A copy of pending claims 1 through 13 is attached hereto as Appendix 1.

IV. Status of Amendments

All amendments to the claims submitted by Appellants during prosecution of this case have been entered upon this appeal. Appellants have attached hereto as Appendix 2 a claim set of claims 1 through 13 incorporating proposed amendments as discussed below in the section entitled **Arguments.**

V. Summary of the Invention

The claimed invention is a method for elucidating the function of proteins and protein domains by generating and examining their three dimensional structures, and more specifically by the use of bioinformatics, molecular biology and nuclear magnetic resonance spectroscopy to enable the rapid and automated determination of functions, as a means for genome analysis. In this method, the first step of the instant method involves identifying a putative polypeptide domain that properly folds into a stable polypeptide domain having a defined three dimensional structure. This identification step involving a domain is taught at pages 11-18 and Figure 1 of the specification as filed. In the second step of the claimed method, the three dimensional structure of the stable polypeptide domain is then determined. Methods for determining the three dimensional structure of the stable polypeptide domain are taught at pages 3-5 and pages 24-25, and include the preferred method NOESY-Assign process, as well as other methods for analysis of NMR data. The next step involves comparing the determined three dimensional structure of the stable polypeptide domain to known three dimensional structures in a protein data bank in order to identify known structures within the protein data bank that may be homologous to the determined three dimensional structure. This step in the method is discussed at page 26. The final step in the claimed method involves correlating a biochemical function

corresponding to the identified homologous structure to a biochemical function for the stable polypeptide domain. This part of the method is described at pages 26-28. Further, the method of the present invention is shown graphically as a flow chart in Figure 1.

VI. Issues

The issues on appeal are :

1) whether the claims of the instant application can properly receive the benefit of priority to the parent application 09/181,601;

2) whether claim 12 is anticipated by 35 U.S.C. 102(b) as being anticipated by the University of Texas at Galveston as evidenced by Mumenthaler et al. (1995);

3) whether claims 1, 5 and 11 are unpatentable under 35 U.S.C. § 103(a) as being obvious over Wallace et al. (1996), in view of Mumenthaler et al. (1995);

4) whether claims 1-5 and 11 are unpatentable under 35 U.S.C. § 103(a) as being obvious over Wallace et al. (1996), in view of Mumenthaler et al. (1995), and further in view of Farber et al. (1992);

5) whether claims 1, 5, 6 and 11 are unpatentable under 35 U.S.C. § 103(a) as being obvious over Wallace et al. (1996), in

view of Mumenthaler et al. (1995), and further in view of Friedrichs et al. (1994);

6) whether claims 1, 5, 7 and 11 are unpatentable under 35 U.S.C. § 103(a) as being obvious over Wallace et al. (1996), in view of Mumenthaler et al. (1995), and further in view of Bagby et al. (1997);

7) whether claims 1, 5 and 8-11 are unpatentable under 35 U.S.C. § 103(a) as being obvious over Wallace et al. (1996), in view of Mumenthaler et al. (1995), and further in view of Holm et al. (1995); and

8) whether claims 1, 5, 8-11 and 13 are unpatentable under 35 U.S.C. § 103(a) as being obvious over Wallace et al. (1996), in view of Mumenthaler et al. (1995), and further in view of Holm et al. (1995) and Farber et al. (1992).

VII. Grouping of Claims

Claims 1 through 13 stand or fall together on the issue of priority and the issues of obviousness under 35 U.S.C. § 103(a), considering any combination of the cited art. Claim 12 stands and falls alone on the issue of anticipation under 35 U.S.C. § 102(b).

VIII. Arguments

A. Priority

Priority to parent application Serial No. 09/181,601 has not been granted because the Examiner suggests that the parent application lacks descriptive support for the element of "NOESY-assign process". The Examiner suggests that the claims as filed in the instant application are not supported by the parent application. Appellants respectfully disagree with the Examiner's conclusions regarding the benefit of priority.

1. MPEP § 201.08 Allows for Addition of Matter Not Disclosed in the Parent Application

The instant application is a continuation-in-part of the parent application Serial No. 09/181,601. MPEP § 201.08 states that a continuation-in-part may be filed during the lifetime of an earlier nonprovisional application, repeating some substantial portion or all of the earlier nonprovisional application and *adding matter not disclosed* in the said earlier nonprovisional application. The Examiner has suggested, however, that there is no support for the matter added in the instant application, namely the "NOESY-Assign process". Appellants respectfully disagree with the Examiner's assertion that there is no support in the parent application for the matter claimed in instant claims 1-13.

The current application shares a substantial portion of content and as well as most of the exact wording of the claims of the parent application 09/181,601. In particular, the steps of determining a biochemical function of a protein or polypeptide domain are identical. Both applications share the basic steps of identifying a putative polypeptide domain; determining three dimensional structure of the stable polypeptide domain; comparing the determined three dimensional structure of the stable polypeptide domain to known three-dimensional structures in a protein data bank; and correlating a biochemical function corresponding to the identified homologous structure to a biochemical function for the stable polypeptide domain. The limitation of "NOESY-assign process", which was added to claim 1 of this continuation-in-part application, is merely one of many means of **determining the three dimensional structure of the stable polypeptide domain.** Therefore, the NOESY-Assign process, claimed in the continuation-part-application, is one means of "determining the three dimensional structure of the stable polypeptide domain", and was claimed separately in the claims of the instant application as it is the preferred embodiment. Therefore, this continuation-part-application, although disclosing a different means for "determining the three dimensional structure of the stable polypeptide domain", is

entitled to the benefit of priority of the parent application as the parent and instant invention are both drawn to a method of determining biochemical function of a protein or polypeptide domain of unknown function, and both rely on the same step, "determining the three dimensional structure of the stable polypeptide domain", only using different preferred embodiments.

B. Rejection of Claims Under 35 U.S.C. 102(b)

The Examiner has rejected claim 12 under 35 U.S.C. 102(b) as being anticipated by the University of Texas at Galveston as evidenced by Mumenthaler et al. (1995). The Examiner suggests that this campus comprised a computer, an NMR facility with a spectrometer, a data collection device, and computer algorithms to analyze NMR spectra and determine tertiary structure of proteins, including the NOAH program for automated assignment of NOESY spectra, as well as laboratories for expression proteins, access to the Wisconsin programs for parsing target polynucleotides, and Internet access to the Protein Data Bank and the DALI webserver.

1. Summary of the Teachings of the Cited Reference

The University of Texas at Galveston, as evidenced by Mumenthaler et al. (1995) disclose a method for automatically assigning proton-proton NOESY spectra in reference to proteins

of **known function**, specifically dendrotoxin K, α-amylase inhibitor tendamistat, and the DNA-binding domain of the 434 repressor protein. Nowhere does the paper of Mumenthaler et al. teach or suggest the steps of parsing a target polynucleotide into at least one putative domain encoding region nor subsequently expressing said putative domain on which to conduct NMR analysis. Moreover, the proteins analyzed by Mumenthaler et al. had **known functions** to which a three dimensional protein structure was assigned.

2. The Cited Reference Fails to Teach the Limitations of the Claims

In accordance with MPEP § 2131, the reference must teach and every element of the claim in order to anticipate the claim. Mumenthaler et al. do not teach every element of the claimed method. As stated *supra*, this reference fails to teach or suggest the steps of parsing a target polynucleotide into at least one putative domain encoding region and subsequently expressing said putative domain on which to conduct NMR analysis. Further, the paper of Mumenthaler deals only with examining proteins with known functions. In contrast, claim 12 is directed toward the determination of a biological function of a protein or protein domain of **unknown function**. Nowhere, do Mumenthaler et al. teach or suggest a

method for determining biochemical function of a protein or polypeptide domain of **unknown function**. Since Mumenthaler et al. do not teach a method wherein polypeptide domains are identified and expressed and the unknown function of said domain is determined, this reference cannot anticipate claim 12.

However, in an earnest effort to make the claimed invention more clear, Appellants have provided in Appendix 2 a proposed amendment to claim 12 wherein an explicit characteristic has been added that lists a sample containing a protein of unknown function.

C. Rejection of Claims Under 35 U.S.C. 103(a)

There are six pending rejections under 35 U.S.C. 103(a) and each rejection relies on the same primary reference (Wallace et al. 1996). The six separate rejections then involve six different combinations of secondary references.

The Examiner has rejected claims 1, 5 and 11 under 35 U.S.C. § 103(a) as being unpatentable over Wallace et al. (1996), in view of Mumenthaler et al. (1995). The Examiner suggests that it would have been *prima facie* obvious to one of ordinary skill in the art at the time this invention was made to combine the 3-D structural alignment and function determination method of Wallace et al. with the NOESY assignment method of Mumenthaler et al. since Mumenthaler

et al. state "We regard our method as a highly practical tool for automatic calculation of three dimensional protein structures from NMR spectra with minimal human interface (abstract)". The Examiner suggests that an ordinary practitioner would have been motivated to determine the 3-D structures used by Wallace et al. for analysis by the automated method of Mumenthaler et al. since the method is a highly practical tool which results "In practice, the work required to assign NOESY spectra is dramatically reduced by applying our automated method (page 466, column 2)".

Claims 1-5 and 11 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Wallace et al. (1996) in view of Mumenthaler et al. (1995) and further in view of Farber et al. (1992). The Examiner suggests that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Wallace et al. in view of Mumenthaler et al. with the database preparation method of Farber et al. since Farber et al. note "Simple neural networks predict coding regions in DNA very well when trained on representation of DNA using single codon frequencies (Page 478, column 1)." The Examiner suggests that an ordinary practitioner would have been motivated to combine the method of Wallace et al. in view of Mumenthaler et al. with the protein coding determinations of Farber et al. in order to maximize the usable

databases to identify homologous proteins and thereby determine the function of unknown proteins.

Claims 1, 5, 6 and 11 have also been rejected under 35 U.S.C. § 103(a) as being unpatentable over Wallace et al. (1996) in view of Mumenthaler et al. (1995) and further in view of Friedrichs et al. (1994). The Examiner suggests that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the 3-D structural alignment and function determination method of Wallace et al. in view of Mumenthaler et al. with the use of NMR structural determination of Friedrichs et al. since Wallace et al. state "This suggests that the development of databases of 3-D templates, such as those that currently exist for protein sequence templates, will help identify the functions of new protein structures as they are determined and pinpoint their functionally important regions (abstract)". The Examiner suggests that the ordinary practitioner would have been motivated to utilize NMR to determine protein structures in order to sensitively and accurately provide data for 3-D determinations and would have been motivated to utilize the automated assignments of Friedrichs et al. in order to minimize the time needed to determine the 3-D structure as expressly motivated by Friedrichs et al.

Claims 1, 5, 7 and 11 have also been rejected under 35 U.S.C. § 103(a) as being unpatentable over Wallace et al. (1996) in view

of Mumenthaler et al. (1995) and further in view of Bagby et al. (1997). The Examiner suggests that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the button test of Bagby et al. with the NMR and functional determination method of Wallace et al. in view of Mumenthaler et al. since Bagby et al. state "The button test is an efficient, small scale way of tackling this problem (page 281, column 1)". The Examiner suggests that the ordinary practitioner would have been motivated to utilize the button test to optimize solubility for NMR since it is expressly noted as efficient and small scale, which reduced time and wasted reagents, which for purified proteins can represent a large investment of time and money.

Claims 1, 5 and 8-11 have also been rejected under 35 U.S.C. § 103(a) as being unpatentable over Wallace et al. (1996) in view of Mumenthaler et al. (1995) and further in view of Holm et al. (1995). The Examiner suggests that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the 3-D structural alignment and function determination method of Wallace et al. in view of Mumenthaler et al. with the NMR technique taught by Holm et al. and well known in the art for structure determination purposes and with the use of domains within the range of 50-300 amino acids since Holm et al. teach screening domain of those sizes. The Examiner

suggests that the ordinary practitioner would have been motivated to utilize database analysis of Holm et al. in mind of Wallace et al. since Wallace et al. state "As the number of known protein structures increases, so the need for a 3-D equivalent of PROSITE grows with it, especially for likely functions of proteins whose biological role is unknown (page 1001, column 1)." Further, Wallace et al. note that there is a need for methods of 3-D comparison of proteins in order to determine the biochemical function of unknown proteins. Holm et al. state "At the last stages of solving a new protein structure, crystallographers and nuclear magnetic resonance (NMR) spectroscopists are keen to know if their structure represents a unique protein fold or if it has an unexpected structural similarity to a known protein fold. To answer these questions, the DALI server performs a database search with a new structure against all structures in the Protein Data Bank (Page 478, column 3)". Thus, the Examiner further suggests that the ordinary practitioner would have been motivated to perform a comparison to determine the relationship of the new protein with proteins present in the database, thereby fulfilling the stated need and motivation of Wallace et al.

Claims 1, 5, 8-11 and 13 have also been rejected under 35 U.S.C. § 103(a) as being unpatentable over Wallace et al. (1996) in view of Mumenthaler et al. (1995) and further in view of Holm et al. (1995) and further in view of Farber et al. (1992). The

Examiner suggests that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Wallace et al. in view of Mumenthaler et al. and further in view of Holm et al. with the database preparation method of Farber et al. since Farber et al. note "Simple neural networks predict coding regions in DNA very well when trained on a representation of DNA using single codon frequencies (page 478, column)." The Examiner further suggests that the ordinary practitioner would have been motivated to combine the method of Wallace et al. in view of Mumenthaler et al. and further in view of Holm et al. with the protein coding determinations of Farber et al. in order to maximize the usable databases to identify homologous proteins and thereby determine the function of unknown proteins.

Appellant respectfully disagrees with the Examiner's suggestions regarding each of the six rejections under 35 U.S.C. 103(a) that are on appeal.

1. Summary of the Teachings of Each Reference Cited Under 35 U.S.C. 103(a)

The primary reference of Wallace et al. does not teach an essential step in the methods of the instant claims, namely the identification of a protein or polypeptide domain that properly folds into a stable polypeptide domain with a defined

three dimensional structure. Nor is there any suggestion of this step, as Wallace et al. (1996) teach derivation of 3-dimensional coordinate templates that have been derived from known 3-dimensional protein structures which are provided in a database. The paper then teaches determination of biochemical function based on the existence of the known 3-dimensional structures. The critical step in the method is the identification of a triad of amino acids (*e.g.*, Ser-His-Asp), that occur in a 3-dimensional configuration to form an active site or "domain". This "domain" concept is completely different from the structural domain concept taught in the instant application. Moreover, no other size of a putative domain is taught or suggested by this reference. In fact, it is this 3 amino acid sequence that is then used to guide identification of the functions of the unknown proteins as the authors report that this triad (3 amino acid domain) is what is critical for differentiating catalytic from non-catalytic proteins among the serine proteases and lipases. Further, as the authors state at page 1002, last paragraph in the first column, their method had specific steps that involved using a data set of serine proteases and lipases to automatically compute a highly specific 3D template for the Ser-His-Asp catalytic triad in the set of proteins. As they also state at page 1002, top of the second column, their method differed

from other previous methods as a simple template specific to the Ser-His-Asp catalytic triad is derived. Then, the next step was to search for similar triads in other proteins to see how often they occurred outside of the serine proteases and lipases. Thus, the teaching of this paper is limited to teaching a skilled artisan that databases may be searched using a specific 3D template, the triad, and then used to identify a potential biological function of a protein with an **unknown structure**. Nowhere does this paper teach or suggest determination of the unknown structure of a protein of **unknown function**. Therefore, this primary reference fails to teach the limitations of independent claim 1, and teaches away from essential elements of claim 1.

Further, nowhere does the primary reference teach or provide the skilled artisan with the motivation to take a single- or multi-domain protein or polypeptide of unknown function and identify each individual domain of said protein or polypeptide. Thus, the primary reference also fails to provide any teaching or suggestion of the system of independent claim 13 which comprises the identification of at least one putative polypeptide domain (element A) prior to the steps of expressing the domain and determining its three dimensional structure.

Accordingly, this primary reference, which is the foundation for rejection of two of the independent claims, claims 1 and 13, fails to teach the limitations of those claims.

Mumenthaler et al. (1995) disclose a method for automatically assigning proton-proton NOESY spectra in reference to proteins of **known function**, specifically dendrotoxin K, α-amylase inhibitor tendamistat, and the DNA-binding domain of the 434 repressor protein. Nowhere does the paper of Mumenthaler et al. teach or suggest the essential step of identifying protein or polypeptide domains. Moreover, the proteins analyzed by Mumenthaler et al. had **known functions** to which a three dimensional protein structure was assigned.

Holm et al. (1995) is a commentary article wherein the DALI method is disclosed as being useful for the study of protein structure. In this method, structural relatedness is measured in terms of similarities of intramolecular distance matrices. The importance of this new automated method is discussed. However, this paper fails to teach a method which has any specific steps at all. Accordingly, this reference provides no teaching or suggestion with respect to either identification of protein or polypeptide domains or the

determination of unknown function of unknown three-dimensional protein structures as claimed in the instant invention.

Farber et al. (1992) disclose a neural network and information theory for determination of coding regions of DNA sequence. This paper, from a different art area (not protein biochemistry as is the area of one of skill in the instant invention), fails to teach or suggest a method such as the claimed invention. Nowhere is there any teaching or suggestion of the identification of protein or polypeptide domains. Moreover, being in a different art area, this paper would not be one that would be used by one of skill in protein biochemistry as motivation to produce the method of the instant invention. Only the hindsight vision afforded by the claimed invention would motivate the skilled practitioner to combine the teachings of Farber et al. with any of the other cited references from the protein biochemistry area (*e.g.*, Wallace et al.)

Friedrichs et al. (1992) is a review type paper that teaches an automated NMR procedure for protein ^{15}N, ^{13}C, and ^{1}H NMR resonance assignments from a set of three-dimensional NMR spectra. While resonance assignments are useful in establishing the three dimensional structure of protein, this information alone is insufficient for three dimensional structure determination. This paper fails to teach or suggest

a method with specific steps such as is claimed in the instant invention. In particular, there is no teaching with respect to either identification of protein or polypeptide domains or the process of determining the 3D structure of a protein, or the determination of unknown function of unknown three-dimensional protein structures as claimed in the instant invention.

Bagby et al. (1997) teaches methods for preparing samples for NMR analysis, specifically a button test method. This method is used by the authors to screen solution conditions to determine conditions under which a protein is soluble at high concentrations that are used for NMR spectroscopy. This paper fails to teach or suggest a method with specific steps such as is claimed in the instant invention. In particular, this paper fails to teach the identification of protein or polypeptide domains, or the process of determining the 3D structure of a protein, or the determination of unknown function of unknown three-dimensional protein structures as claimed in the instant invention.

Therefore, Appellant respectfully disagrees with the Examiner's suggestion that any combination of these prior art references establishes a *prima case* of obviousness.

2. If an Independent Claim is Nonobvious Then a Claim Depending Therefrom is Nonobvious (MPEP 2143.03)

Appellants point out as well that under MPEP 2143.03, "If an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious (In re Fine, 837 F.2d 1071, 5 USPQ2d 1596, Fed. Cir. 1988)." Thus, while some of the secondary references may teach or suggest specific elements as set forth in the dependent claims, the cited combination of references fail to teach or suggest all the limitations of the method or system as set forth in independent claims 1, 12 and 13.

3. Three Basic Criteria of *prima facie* Obviousness

In accordance with MPEP § 2143, to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the reference itself or in the knowledge generally available to one of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all of the claim limitations. The prior art combinations cited under 35 U.S.C. 103 by the Examiner fail to teach or suggest all of the limitations of the claims and fail to provide either the

motivation to modify the reference or the expectation of success.

4. The Cited Art Fails to Teach the Limitations of the Claims

Any of the combinations of prior art fail to teach or suggest the limitations in the claims. In particular, and as discussed *supra*, none of the cited references, either alone or when combined, teach the determination of the function of a protein of **unknown function** wherein this is accomplished by determining the structure of the protein and then correlating the structure with a function when the function is also unknown. Both the MPEP and case law are quite clear. To establish *prima facie* obviousness of a claimed invention, all the limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974) and MPEP 2143.03.

5. The Combined References Fail to Provide Motivation

The cited combinations of references also fail to establish a *prima facie* case of obviousness because the motivation to combine these references is lacking. The teaching or suggestion must be found in the prior art and not based on applicant's disclosure. In re Vacek, 947 F.2d 488,

20 USPQ2d 1438 (Fed. Cir. 1991). The mere fact that references <u>can</u> be combined or modified does not render the resultant combination obvious unless the prior art suggests the desirability of the combination. MPEP § 2143.01. *In re Mills,* 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). Wallace et al. is a protein biochemistry article directed at the analysis of protein structure and function. Contrary to the Examiner's suggestion, it would not have been obvious to the ordinary protein biochemist after reading Wallace et al. to take the additional steps provided by Farber et al. of mining a polynucleotide database. Furthermore, the combination of Wallace et al. with Farber et al. still does not provide the essential step of identifying protein or polypeptide domains. Moreover, the "catalytic triad domain" described by Wallace et al. is distinct from the overall "structural domains" of the instant invention. Thus, Farber et al. alone is insufficient for determination of unknown function of unknown three-dimensional protein structures as claimed in the instant invention.

Therefore, solely on the basis of the requirements for establishing a *prima facie* case of obviousness (MPEP 2143), any of the combinations of the cited references fail to make obvious any of the pending claims.

6. The Cited References Fail to Provide a Reasonable Expectation of Success

The primary reference cited in each of the six obviousness rejections, Wallace et al. (1996), is also important in that it would actually teach away from an expectation of success for the present method. The method of Wallace et al. is based on the importance of the identification of the triad domain. It is only with use of this domain as a screening tool that the authors report any success at correlating structure of a protein with a function. The present method, however, is not based on this triad, and in fact is based on a very different type of domain. Accordingly, this primary reference wold lead one of skill to not expect success using the current method which is not limited to use of the triad disclosed by Wallace et al.

Therefore, solely on the basis of the requirements for establishing a *prima facie* case of obviousness (MPEP 2143), these combined references, in any cited combination, fail to make obvious any of the pending claims.

IX. Conclusion

The references cited by the Examiner clearly do not provide the requisite teaching or suggestion to render the claimed invention of claims 1-11 or 13 obvious. Further the reference

cited by the Examiner fails to anticipate claim 12. Finally, Appellants respectfully disagree with the Examiner's conclusions regarding the assignment of priority and request reconsideration of the benefit of priority.

Respectfully submitted,

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Appendix 1 - Pending Claims

Claim 1: A high-throughput method for determining the biochemical function of a protein or polypeptide domain of unknown function comprising:

(A) identifying a putative polypeptide domain that properly folds into a stable polypeptide domain, said stable polypeptide domain having a defined three dimensional structure;

(B) determining three dimensional structure of the stable polypeptide domain from an automated analysis of NMR spectrometer spectra of said polypeptide domain, wherein said automated analysis is conducted by a NOESY-Assign process;

(C) comparing the determined three dimensional structure of the stable polypeptide domain to known three-dimensional structures in a protein data bank, wherein said comparison identifies known structures within said protein data bank that are homologous to the determined three dimensional structure; and

(D) correlating a biochemical function corresponding to the identified homologous structure to a biochemical function for the stable polypeptide domain.

Claim 2: The method of claim 1, further comprising the pre-step of parsing a target polynucleotide into at least one putative polypeptide domain.

Claim 3: The method according to claim 2, wherein said parsing is performed by a first computer algorithm, wherein said first computer algorithm is selected from the group consisting of a computer algorithm capable of determining exon phase boundaries of a polynucleotide, and a computer algorithm capable of determining interdomain boundaries encoded in a polynucleotide.

Claim 4: The method of claim 3, further comprising a computer algorithm that compares the putative polypeptide domain sequence with known domain sequences stored within a database.

Claim 5: the method of claim 1, wherein said NMR spectra are analyzed by a second computer algorithm that automatically assigns resonance assignments to the polypeptide sequence.

Claim 6: The method of claim 1, wherein said identification of said stable polypeptide domain comprises measuring the time course of amide hydrogen-deuterium exchange.

Claim 7: The method of claim 1, wherein prior to step (B), said stable polypeptide domain is optimally solubilized, said optimum solubilization comprising:

I) preparing an array of microdialysis buttons, wherein each of said microdialysis buttons contains at least 1 µl of an approximately 1 mM solution of said stable polypeptide domain;

ii) dialyzing each member of said array of microdialysis buttons against a different dialysis buffer;

iii) analyzing each of said dialyzed microdialysis buttons to determine whether said stable polypeptide domain has remained soluble; and

iv) selecting the polypeptide domain having optimum solubility characteristics for NMR spectroscopy.

Claim 8: The method of claim 1, wherein said comparison of said determined three dimensional structure to said three dimensional structures in the protein data bank is performed by a third computer algorithm that is capable of determining 3D structure homology between said determined three dimensional structure and a member of said PDB.

Claim 9: The method of claim 8, wherein said third computer algorithm is selected from the group consisting of DALI, CATH and VAST.

Claim 10: The method of claim 1, wherein said protein data bank is Protein Data Base ("PDB").

Claim 11: The method of claim 4, wherein said database contains domain sequence information of known and determined domain sequences.

Claim 12: An integrated system for rapid determination of a biochemical function of a protein or protein domain of unknown function:

(A) a first computer algorithm capable of parsing said target polynucleotide into at least one putative domain encoding region;

(B) a designated lab for expressing said putative domain;

(C) an NMR spectrometer for determining individual spin resonances of amino acids of said putative domain;

(D) a data collection device capable of collecting NMR spectral data, wherein said data collection device is operatively coupled to said NMR spectrometer;

(E) at least one computer;

(F) a second computer algorithm capable of assigning individual spin resonances to individual amino acids of a polypeptide;

(G) a third computer algorithm capable of determining tertiary structure of a polypeptide, wherein said polypeptide has had resonances assigned to individual amino acids of said polypeptide;

(H) a database, wherein stored within said database is information about the structure and function of known proteins and determined proteins; and

(I) a fourth computer algorithm capable of determining 3D structure homology between the determined three dimensional structure of a polypeptide of unknown function to three dimensional structure of a protein of known function, wherein said protein of known structure is stored within said protein database, wherein said fourth computer algorithm determines said structure by an automated NOESY-Assign process.

Claim 13: A high-throughput method for determining a biochemical function of a polypeptide of unknown function encoded by a target polynucleotide comprising the steps:

(A) identifying at least one putative polypeptide domain encoding region of the target polynucleotide ("parsing");

(B) expressing said putative polypeptide domain;

(C) determining whether said expressed putative polypeptide domain forms a stable polypeptide domain having a defined three dimensional structure ("trapping");

(D) determining the three dimensional structure of the stable polypeptide domain by an automated NOESY-Assign process;

(E) comparing the determined three dimensional structure of the stable polypeptide domain to known three dimensional structures in a Protein Data Bank to determine whether any such known structures are homologous to the determined structure; and

(F) correlating a biochemical function corresponding to the homologous structure to a biochemical function for the stable polypeptide domain.

Appendix 2 - Proposed Amendments to Claims 1, 12 and 13

Claim 1: A high-throughput method for determining the biochemical function of a protein or polypeptide domain of unknown function comprising:

(A) obtaining a sample comprising a protein of unknown function and identifying a putative polypeptide domain within said protein that properly folds into a stable polypeptide domain, said stable polypeptide domain having a defined three dimensional structure;

(B) determining three dimensional structure of the stable polypeptide domain from an automated analysis of NMR spectrometer spectra of said polypeptide domain, wherein said automated analysis is conducted by a NOESY-Assign process;

(C) comparing the determined three dimensional structure of the stable polypeptide domain to known three-dimensional structures in a protein data bank, wherein said comparison identifies known structures within said protein data bank that are homologous to the determined three dimensional structure; and

(D) correlating a biochemical function corresponding to the identified homologous or analogous structure to a biochemical function for the stable polypeptide domain.

Claim 2: The method of claim 1, further comprising the pre-step of parsing a target polynucleotide into at least one putative polypeptide domain.

Claim 3: The method according to claim 2, wherein said parsing is performed by a first computer algorithm, wherein said first computer algorithm is selected from the group consisting of a computer algorithm capable of determining exon phase boundaries of a polynucleotide, and a computer algorithm capable of determining interdomain boundaries encoded in a polynucleotide.

Claim 4: The method of claim 3, further comprising a computer algorithm that compares the putative polypeptide domain sequence with known domain sequences stored within a database.

Claim 5: the method of claim 1, wherein said NMR spectra are analyzed by a second computer algorithm that automatically assigns resonance assignments to the polypeptide sequence.

Claim 6: The method of claim 1, wherein said identification of said stable polypeptide domain comprises measuring the time course of amide hydrogen-deuterium exchange.

Claim 7: The method of claim 1, wherein prior to step (B), said stable polypeptide domain is optimally solubilized, said optimum solubilization comprising:

I) preparing an array of microdialysis buttons, wherein each of said microdialysis buttons contains at least 1 µl of an approximately 1 mM solution of said stable polypeptide domain;

ii) dialyzing each member of said array of microdialysis buttons against a different dialysis buffer;

iii) analyzing each of said dialyzed microdialysis buttons to determine whether said stable polypeptide domain has remained soluble; and

iv) selecting the polypeptide domain having optimum solubility characteristics for NMR spectroscopy.

Claim 8: The method of claim 1, wherein said comparison of said determined three dimensional structure to said three dimensional structures in the protein data bank is performed by a third computer algorithm that is capable of determining 3D structure homology between said determined three dimensional structure and a member of said PDB.

Claim 9: The method of claim 8, wherein said third computer algorithm is selected from the group consisting of DALI, CATH and VAST.

Claim 10: The method of claim 1, wherein said protein data bank is Protein Data Base ("PDB").

Claim 11: The method of claim 4, wherein said database contains domain sequence information of known and determined domain sequences.

Claim 12: An integrated system for rapid determination of a biochemical function of a protein or protein domain of unknown function consisting of:

(A) a first computer algorithm capable of parsing ~~said~~ a target polynucleotide encoding a protein of unknown function into at least one putative domain encoding region;

(B) a designated lab for expressing said putative domain;

(C) an NMR spectrometer for determining individual spin resonances of amino acids of said putative domain;

(D) a data collection device capable of collecting NMR spectral data, wherein said data collection device is operatively coupled to said NMR spectrometer;

(E) at least one computer;

(F) a second computer algorithm capable of assigning individual spin resonances to individual amino acids of a polypeptide;

(G) a third computer algorithm capable of determining tertiary structure of a polypeptide, wherein said polypeptide has had resonances assigned to individual amino acids of said polypeptide;

(H) a database, wherein stored within said database is information about the structure and function of known proteins and determined proteins; and

(I) a fourth computer algorithm capable of determining 3D structure homology between the determined three dimensional structure of ~~a~~ said polypeptide encoding said protein of unknown function to the known three dimensional structure of a polypeptide encoding a protein of known function, wherein said protein of known structure is stored within said protein

database, wherein said fourth computer algorithm determines said structure by an automated NOESY-Assign process.

Claim 13: A high-throughput method for determining a biochemical function of a ~~polypeptide~~ protein of unknown function encoded by a target polynucleotide comprising the steps:

(A) obtaining a sample of a target protein of unknown function and identifying at least one putative polypeptide domain encoding region of the target ~~polynucleotide~~ protein ("parsing");

(B) expressing said putative polypeptide domain;

(C) determining whether said expressed putative polypeptide domain forms a stable polypeptide domain having a defined three dimensional structure ("trapping");

(D) determining the three dimensional structure of the stable polypeptide domain by an automated NOESY-Assign process;

(E) comparing the determined three dimensional structure of the stable polypeptide domain to known three dimensional structures in a Protein Data Bank to determine whether any such known structures are homologous to the determined structure; and

(F) correlating a biochemical function corresponding to the homologous structure to a biochemical function for the stable polypeptide domain.